



Patent  
Attorney's Docket No. 010091-037

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Patent Application of

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Nadeau et al.

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Group Art Unit: 1634

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REISSUE Application No.: 09/082,247

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Examiner: S. Houtteman

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Filed: May 20, 1998

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For: METHOD FOR DETECTING A  
TARGET NUCLEIC ACID

**RECEIVED**

**PROTEST UNDER 37 CFR §1.291(a)**

**JAN 05 1999**

**MATRIX CUSTOMER  
SERVICE CENTER**

Assistant Commissioner for Patents  
Washington, D.C. 20231

ATTENTION: Mr. John Doll, Director, Group 1630

Sir:

A copy of this protest has been served upon the agent of the above-named Applicant pursuant to 37 CFR §1.291(a) as verified by the attached Certificate of Service. In addition, an Information Disclosure Statement is concurrently submitted which lists all documents relied upon herein and the relevance of each. Accordingly, entry and consideration of this protest into the above-referenced application is respectfully requested.

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REMARKS

JAN 05 1999

*MAT RABUCHI/UFER  
SEARCH CENTER*

This protest is submitted in response to the reissue application noted above, in order to point out the unpatentable nature of several of the newly submitted claims. Specifically, newly submitted Claims 26 and 36 are neither described nor enabled by the original specification according to the requirements of 35 U.S.C. §112, first paragraph. In addition, Claims 43-50 are clearly anticipated by the prior art, at least part of which is attached hereto, and are therefore unpatentable under 35 U.S.C. §102.

According to the Declaration under 37 CFR §1.175 and Power of Attorney filed concurrently with the present application, this request for reissue was filed for the following reasons:

- (i) the Applicants believed the original claims were "mistakenly limited . . . [to] only *methods* for concurrently generating a secondary amplification product and an amplification product; and
- (ii) the Applicants "mistakenly limited all [original] claims to specify one embodiment of a Strand Displacement Amplification (SDA) reaction with its requisite components." (With emphasis.)

In addition, the Assent of Assignee filed under 37 CFR §1.172(a) appears to confirm these reasons for filing the reissue claims, namely that the Applicants "mistakenly limited all claims to specifying only methods or a particular embodiment of a Strand Displacement (SDA) Reaction."

To correct these alleged defects, new Claims 21-50 have been submitted which appear to address the alleged deficiencies in the following manner:

- (i) New Claims 43-50 were added which expand the invention to include claims directed to signal primers apparently for use in the disclosed methods; and
- (ii) Independent Claims 21 and 29 were added which correspond to original independent Claims 1 and 8, except that new independent Claims 21 and 29 broadly encompass any "nucleic acid amplification reaction" involving the claimed steps rather than solely a "Strand Displacement Reaction" per se. Dependent claims were also added which refer back to the new claims, and almost completely correspond to and parallel the dependency of original dependent Claims 2-7 and 9-20.

However, there is a third, extremely important change submitted in the new claims which Applicants fail to point out in either the Declaration or Assent by Assignee. To the extent that the Oath/ Declaration points out "at least one error" relied upon to support reissue, it appears to satisfy the requirements of 35 U.S.C. §251. However, it would have been a good faith gesture for the Applicants to also point out this crucial and significant third change in the new claims so that it would be not be missed during examination. This protest respectfully requests that the Examiner take notice of this third change in the claims and give it his careful consideration during this reissue prosecution.

This protest will address the enablement issues of this third change in the claims first, and then return to the other changes in the claims listed above and noted by Applicants in the Reissue Oath/ Declaration.

Specifically, the third change in the patented claims not noted in the Reissue oath involves a further broadening of the subject matter included in the new claims. The broadening of the claims is apparent when one compares original Claims 6 and 15 with newly submitted Claims 26/ 27 and 36/37. For the Examiner's convenience, the claims are reproduced below:

Original Claims	New Claims
6. The method of claim 5 wherein the secondary amplification product is detected by cleaving the restriction endonuclease recognition site with a restriction endonuclease to generate a cleavage product, separating the cleavage product on the basis of size, and detecting the cleavage product.	26. The method of claim 25 wherein the secondary amplification product is detected by cleaving the restriction endonuclease recognition site with a restriction endonuclease to generate a cleavage product.  27. The method of claim 26 wherein the secondary amplification product is detected by separating the cleavage product on the basis of size and detecting the cleavage product.
15. The method of claim 14 wherein the secondary amplification product is detected by cleaving the restriction endonuclease recognition site with a restriction endonuclease to generate a cleavage product, separating the cleavage product on the basis of size, and detecting the cleavage product.	36. The method of claim 35 wherein the secondary amplification product is detected by cleaving the restriction endonuclease recognition site with a restriction endonuclease to generate a cleavage product.  37. The method of claim 36 wherein the secondary amplification product is detected by separating the cleavage product on the basis of size and detecting the cleavage product.

The new claims reproduced above are dependent on the newly submitted independent Claims 21 and 29 in essentially the same manner as are original Claims 6 and 15 dependent on the original independent Claims 1 and 8. For instance, while Claims 6 and 15 are indirectly dependent on the original independent method claims directed to methods for concurrently generating a secondary amplification product and

an amplification product in a Strand Displacement Amplification (SDA) reaction, the new claims depend in the same manner from newly submitted independent claims directed to methods for concurrently generating a secondary amplification product and an amplification product during a "nucleic acid amplification reaction" in general having the recited steps.

However, the new claims differ from original Claims 6 and 15 in that the limitation of "detecting by cleaving the restriction endonuclease recognition site" (Claims 26 and 36) is separated from the limitation of "separating the cleavage product on the basis of size" (Claims 27 and 37). This division of limitations in effect allows new Claims 26 and 36 to read on a method of detecting a restriction endonuclease cleavage reaction which does not require separation of the cleavage products. As this protest will now show, such a method is clearly not enabled by the specification of the above-referenced application.

In order to comprehend how the above-referenced application fails to enable the method as now claimed in new Claims 26 and 36, it is important to first envision what is occurring in general during an amplification reaction, and develop an understanding as to what is required for detection of restriction endonuclease cleavage products absent separation of the products. First, as described in column 1, paragraph 2 of the reissue application,

Primer-based detection of amplified nucleic acid reactions in PCR often relies on incorporation of an amplification primer into the amplification product during the amplification reaction. Features engineered into the PCR amplification primer therefore appear in the amplification product and can be used either to detect the amplified target sequence or to immobilize the amplicon for detection by other means.

The disclosure offers several examples of "features" that can be engineered into the amplification primer that can subsequently be used to detect an amplification product. For instance, as described in columns 1-2 of the specification, biotin-containing primers with and without other labels such as fluorescent dyes are known in the prior art, and have been incorporated into primers used for nucleic acid amplification reactions to facilitate detection of amplification products. However, these methods require separation or capture of the amplification product via the biotin moiety.

In specific working examples of the disclosure (Examples 1-3), Applicants demonstrate various ways to affect detection of a <sup>32</sup>P-labeled primer and subsequent extension product formed therefrom in the specifically disclosed nucleic acid amplification reaction, i.e., Strand Displacement, whereby detection of a secondary amplification product is used to monitor the reaction. However, the three Examples employ detection of the <sup>32</sup>P label following gel electrophoresis, filtration using a microconcentrator and capture via a biotin moiety, respectively. All of these methods require separation of the amplification product.

The reason separation is required for detection of  $^{32}\text{P}$ -labeled reaction products is clear. There is no increase in the amount of radioactivity from a  $^{32}\text{P}$  label during an amplification reaction. The only basis for distinction is that, as the amplification reaction proceeds, the label becomes incorporated into the amplification product. But if the product is not separated from unextended primers, there is no way to determine if the amplification reaction was successful, because there is no way to distinguish the  $^{32}\text{P}$  label of an unextended primer from a label incorporated into an amplification product in the same reaction tube on the basis of the radioactive signal alone. Thus, it is clear that the reaction products of the specifically exemplified embodiments cannot be detected via the disclosed  $^{32}\text{P}$  label alone without some sort of separation step.

The application does mention one technique which might be used to detect reaction products absent capture or separation. In column 8 of the reissue application, first paragraph, in reference to "structure #5" it is stated that such a structure "may be detectable when the reporter group is detectable independent of capture, e.g., when the reporter is a fluorescent label detectable by anisotropy or fluorescence polarization." The same passage references a PCT application WO 92/18650. According to Figure 1 and column 7, last paragraph, "structure #5" is a double stranded reaction product, and according to the cited PCT (attached hereto in the Information Disclosure Statement), amplification products may be detected by the increase in fluorescence polarization which occurs upon hybridization of a fluorescently labeled probe.

For instance, as described on page 7 of the cited PCT, lines 16-23:

The method of [the] invention comprises incubation of denatured amplified nucleic acids under hybridizing conditions with a nucleic acid probe of homologous sequence covalently coupled to a fluorophor. The fluorophor-conjugated probe is added at a concentration sufficient to produce a measurable increase in fluorescence polarization when hybridized to the amplified nucleic acid sequences. (Emphasis added.)

Thus, the reference cited in the instant application mentions nothing about the specific detection of a restriction endonuclease cleavage product using fluorescence or any other detection method, and in fact could not be used to distinguish a cleavage reaction product from a nucleic acid amplification product since the increase in fluorescence reportedly occurs upon initial hybridization of the primer according to PCT WO 92/18650.

Moreover, it is clear upon a reading of the instant specification that concurrent detection of restriction products, i.e, without separation of the cleavage products, was neither contemplated nor intended. For instance, as stated in the sentence bridging columns 5 and 6, “[n]ucleotide sequences which result in double stranded restriction endonuclease recognition sites are a preferred structural feature for use in signal primers, as subsequent restriction may be used to generate a secondary amplification product which is recognizable by a characteristic size” (emphasis added). Thus, the specific embodiment employing detection via cleavage by a restriction endonuclease requires

separation of the cleavage products such that size is discernable, because no other means to detect the cleavage products is contemplated, disclosed or implied by the specification.

Since its inception, the Court of Appeals for the Federal Circuit has frequently addressed the "written description" requirement of §112. A fairly uniform standard for determining compliance with the "written description" requirement has been maintained throughout: Although the applicant does not have to describe exactly the subject matter claimed, the description must clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed. The test for sufficiency of support in a parent application is whether the disclosure of the application relied upon reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991). Wang Laboratories Inc. v. Toshiba Corporation, 26 USPQ2d 1767, 1774 (Fed. Cir. 1993). It would appear from the above review of what the present specification actually teaches, the skilled artisan would certainly not believe that the Applicants were in possession of the subject matter as broadly recited in Claims 26 and 36.

Thus, if the present specification clearly indicates that Applicants had not contemplated the newly claimed subject matter, it is not immediately clear why Applicants would separate the limitations set forth in original Claims 6 and 15 such that new Claims 26 and 36 encompass methods of detecting restriction endonuclease cleavage products without separation. Moreover, it is not immediately clear why Applicants

would fail to exercise good faith and point this maneuver out to the Examiner for proper consideration. But one might be able to infer what Applicants' intention was based on the following evidence.

On August 17, 1998, Applicant's agent contacted the inventors and assignee of U.S. Patent No. 5,763,181 (also attached in the accompanying Information Disclosure Statement) to arrange a meeting to discuss a possible collaboration or other agreement regarding material in the '181 patent (see attached letter). Although neither the present reissue application nor its parent application are mentioned in this letter, it appears that the assignee of the present application, Becton Dickinson, may have been seeking to obtain patent coverage or negotiate a license agreement regarding the material disclosed in the '181 patent.<sup>1</sup> Becton Dickinson inexplicably declined to follow through with the planned meeting shortly after this letter was received.

The '181 patent discloses detection of restriction endonuclease cleavage products using fluorescence during a wide range of assays, including using such a detection method for continuous monitoring of nucleic acid amplification reactions as they occur. For instance, Claim 1 of the '181 patent reads as follows:

1. A method for detecting **continuously** a nucleic acid cleavage reaction in a fluorometric assay comprising the steps of:

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<sup>1</sup> The letter references a publication and U.S. Patent No. 5,550, 025, both of which are attached hereto and cited in the Information Disclosure Statement accompanying this Protest. However, just as is seen in the present reissue application, neither the cited patent nor the reference enables detection of cleavage products without separation.

- (a) preparing a fluorescently labeled oligonucleotide containing a double-stranded nucleic acid sequence recognizable by said endonuclease, wherein said oligonucleotide acts as a substrate for said endonuclease;
- (b) contacting the oligo of step (a) with said endonuclease in an amount sufficient to cleave said oligonucleotide to produce oligonucleotide products; and
- (c) detecting continuously a nucleic acid cleavage reaction by detecting an increase in fluorescence intensity (with emphasis).

Also, Claim 12 is noted which reads:

12. The method of claim 1, wherein said endonuclease-mediated nucleic acid cleavage reaction occurs during a process for amplifying or detecting a specific DNA or RNA sequence.

The term "continuously" as used in Claim 1 develops meaning in light of the discussion at columns 1-2 of the '181 patent, wherein it is noted that gel electrophoresis analysis of cleavage products is time-consuming and laborious because it is "discontinuous, meaning that the process cannot be monitored throughout the cleavage process" (see col. 1, line 62 to col. 2, line 9). The invention described by the '181 patent overcomes this and other disadvantages of the prior art by enabling detection of the cleavage reaction as it occurs in the reaction tube. No subsequent separation of cleavage products is required.

Enablement of such technology was not as straightforward as the Applicants of the present reissue application would have one believe in submitting claims having the scope encompassed by new Claims 26 and 36. For instance, the '181 patent discloses how to label the oligonucleotides, what factors to consider in choosing fluorophores for

the method and how to monitor changes in fluorescence. The present reissue application does not. The '181 patent teaches what reaction conditions are optimal for detecting changes in fluorescence. The present reissue application does not. In particular, the '181 patent discusses two different embodiments which may be used to design fluorescence based assays. The present reissue application does not. Moreover, the '181 patent describes in particular what linkers may be used to attach the fluorophores to the oligonucleotide primers, and how distance between the fluorophore and the DNA, or between separate fluorophores, can be a significant consideration in designing a detection assay.

For instance, Example 1 of the '181 patent uses a single fluorophore label attached to the oligonucleotide via a six-carbon linker, which is initially quenched before cleavage due to interactions between the fluorophore and the DNA (see col. 20, lines 47-57). However, the second embodiment uses fluorescence energy transfer between a donor fluorophore and an acceptor. Thus, in the second embodiment, fluorescence is quenched until the donor and acceptor are separated by endonuclease cleavage of the oligonucleotide primer, thereby leading to an increase in fluorescence that can be continuously monitored throughout the assay.

But in designing the second embodiment, the inventors of the '181 patent had to carefully consider how far apart on the oligonucleotide to attach the donor and acceptor fluorophores, as well as how to inhibit a quenching interaction between the first

fluorophore and the DNA via the first quenching mechanism such that changes in fluorescence detected using the second embodiment would be an accurate measure of cleavage. The inventors of the '181 patent found that using a twelve carbon linker rather than a six carbon linker to attach the donor fluorophore to the oligonucleotide in the second embodiment was one way to address this concern (see column 20, lines 58-62).

Thus, it is clear that significant experimentation and work went into making the invention of the '181 patent, which is a fair representation of the quantity and type of disclosure required to enable such a technology. It is well established that there must be a reasonable correlation between the scope of the exclusive right granted to a patent applicant and the scope of enablement set forth in the patent application. Ex parte Maizel, 27 USPQ2d 1662, 1665 (BPAI 1993). Clearly, there is no such correlation between the present reissue application and the scope of Claims 26 and 36, particularly when one considers that there is absolutely no mention of any of the above conditions described in the '181 patent which must be carefully considered when practicing the claimed method.

The Board has further discussed the "reasonable correlation" which must exist between the specification and scope of the claims as follows: In cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics, predicted by resort to

known scientific laws. In cases involving unpredictable factors, such as most chemical reactions . . . the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved. Ex Parte Gould, 231 USPQ 949, 952 (PTO Bd. App. & Int. 1986).

A claim which is of such breadth that it reads on subject matter as to which the specification is not enabling should be rejected under the first paragraph of §112. In re Hyatt, 218 USPQ 195, 197 (Fed. Cir. 1983). This protest respectfully requests such a ruling with regard to Claims 26 and 36.

The urgency and importance of this matter are not to be taken lightly. The benefits of the technology disclosed in the '181 patent are nearly limitless. Nucleic acid amplification reactions are used in the food industry to detect microbial contamination, in the medical community to diagnose disease and detect genetic defects, by the Defense departments of our government who use the technology to screen for biological weapons, etc. Fluorescence energy transfer technology enables detection of the amplification reaction as it is occurring; thus, one need not wait for the reaction to finish and run the fragments out on a gel, or separate the fragments by other means for subsequent analysis.

Just imagine being able to go to the doctor's office for a blood test and be able to obtain the results right then and there. Just think what the technology would mean to the food industry, who's process for testing for contaminated food will dramatically decreased. And think about what it would mean for the defense of this country to be able

to detect the presence of a biological hazard in a matter of minutes. It is no wonder then why the Applicants of the present reissue application would like to achieve broad claims which cover such technology in combination with their own Strand Displacement Amplification technique. However, the actual detection method belongs to the owner of the '181 patent and those who obtain a license for such technology by legal means.

The fact that the assignee of the present application has alternative motives for obtaining patent protection for fluorescence energy transfer concurrent detection of amplification reactions is further evidenced by the attached material obtained from Becton Dickinson's website (<http://www.bdms.com/new/newtech/sda/applications.html>). For instance, on page 2 of the website article entitled "Your Premier Tool for Research, Commercial and Clinical Applications," it is stated that "a real-time detection system has been developed utilizing both fluorescence polarization and energy transfer." A graph depicting the results of such a method when used for real-time detection of Chlamydia as provided on the Becton Dickinson website is also attached. Generation of such a graph using energy transfer fluorescence is not enabled by the present reissue application, and the Applicants should not be able to reach back in time to an application filed before the technology was developed in order to obtain an earlier filing date than the party who actually invented the technology. Although the assignee, Becton Dickinson, would clearly like to obtain claims broadly encompassing real time detection of restriction fragment cleavage products using fluorescence energy transfer to protect their new

technology as advertised on the Internet, the present reissue application neither describes or enables such technology.

The fact that the assignee of the present reissue application has been aware of the '181 patent but has not brought it to the attention of the Patent & Trademark Office, particularly in view of the broadened scope of Claims 26 and 36, is further evidence of a clear lack of good faith. In fact, the following excerpt from 37 C.F.R. § 1.56 is respectfully noted:

[N]o patent will be granted on an application in connection with which fraud on the Office was practiced or attempted or the duty of disclosure was violated through bad faith or intentional misconduct.

This Protest respectfully requests that the Patent & Trademark Office recognize the rights which have fairly been earned by the inventors of the '181 patent. Allowance of reissue Claims 26 and 36 would truly be an inequitable injustice to the inventors of the '181 patent who spent years perfecting the disclosed technology, and who the Patent & Trademark Office has already recognized to be the first to enable and describe "real-time" concurrent detection of a restriction enzyme cleavage reaction using fluorescence energy transfer. The Patent & Trademark Office should not allow inventors to use the reissue process to "come in the back door" so to speak and obtain broad claims encompassing a technology that their patent disclosure does not support.

In practice, the rejection of reissue claims has been founded upon either a failure to demonstrate error without deceptive intention, or because the newly submitted claims are not supported by the disclosure of the original patent." In re Amos, 21 USPQ2d 1270, 1274 (Fed. Cir. 1991). Here, it is clear that both situations exist. Therefore, at the very least, the Office is respectfully requested to recognize the invalidity of Claims 26 and 36 under 35 U.S.C. §112, first paragraph.

Turning now to the other reasons that the reissue application was filed, this Protest respectfully notes as a further matter that Claims 43-50 are clearly anticipated by the prior art and should be rejected under 35 U.S.C. §102. Of these claims, Claim 43 is the sole independent claim and reads as follows:

43. A signal primer comprising:

- a) a target binding sequence which hybridizes to a target sequence at a position downstream of the position where a nucleic acid amplification primer hybridizes to the target sequence;
  
- b) a 3' end which is extendable to generate a signal primer extension product, said signal primer extension product displaceable from the target sequence by extension of the nucleic acid amplification primer; and

- c) a means for detecting the signal primer extension product.

The possible "means for detecting the signal primer extension product" are further defined in Claim 44, which indicates that such means may be selected from the group consisting of "size which differs from that of a nucleic acid primer amplification product, chemical modification, special nucleotide sequence, and a structural feature."

The reason these claims are unpatentable over a vast body of prior art is that the claimed "signal primer" reads on any oligonucleotide. The only limitations which attempt to define and distinguish the claimed primer from prior art oligos are matters which contribute to its design, which are specifically chosen based on intended use. It is well settled that the recitation of a new intended use for an old product does not make a claim to that old product patentable. In re Schreiber, 44 USPQ2d 1429, 1431-32 (Fed. Cir. 1997).

For instance, an oligo used to prime an amplification reaction of an internal section of a gene will naturally contain a "target binding sequence which hybridizes to a target sequence at a position downstream of the position where" another nucleic acid amplification primer used to amplify the entire gene would hybridize. Just because the primers are to be used in a Strand Displacement amplification reaction does not make them any different or patentable over two such situated primers used to amplify different sections of any known gene, because intended use does not impart patentability.

Likewise, just because the primer extension product is "displaceable" from the target sequence by extension from another nucleic acid amplification primer does not necessarily make it patentable. Any oligo which anneals downstream and in the way of a transcript initiating from an upstream primer will be displaced when the polymerase enzyme reaches that part of the target template to which it is annealed. Thus, any oligo is displaceable depending on the target and upstream primer it is to be used with, and intended use does not impart patentability.

Finally, the inclusion of "a means for detecting the signal primer extension product," particularly the "means" defined in Claim 44, does not render the claimed primers patentable because such means are known in the art. For instance, "size" becomes a "means" when the products of the amplification reaction are separated on a gel; this is not novel or nonobvious. A "chemical modification" could include virtually anything, including radioactive labels, fluorescent labels and biotin labels, all of which are described in the prior art attached hereto and of record. A "special" nucleotide sequence and "structural feature" are both defined in the specification as including a restriction endonuclease sequence (see bottom of column 5 to top of column 6). Yet primers containing restriction endonuclease sequences are commonly used in nucleic acid amplification reactions to facilitate subsequent cloning of the amplified nucleic acid. So the "means" defined as the third distinguishing limitation of the claimed primers do not impart patentability.

To the extent that Claims 45-49 separately define such means, they also lack novelty and patentability over a wide body of prior art. And, considering that the claimed primers read on any known oligonucleotide primer, the extension product claimed in Claim 50 reads on any known product of a nucleic acid amplification reaction.

This protest will not spend any further time explaining why the claimed signal primers and extension products are not patentable because the protesting party believes this to be an obvious and straightforward matter. In fact, the addition of Claims 43-50 may have in fact been a smoke screen to disguise the real intent of the present reissue, which was likely to obtain an allowance of Claims 26 and 36 through the "back door" process of reissue.

Turning finally to the other specified reason the present reissue was filed, this protest will not address the patentability of the Claims 21 and 29 to the extent that they now read on any nucleic acid amplification reaction having the recited steps rather than a Strand Displacement Amplification reaction per se. This is because the protesting party believes the recited steps alone to be definitive of a Strand Displacement Amplification reaction, and whether or not they are labeled as such has no relevance to the scope of the claim.

This protest respectfully submits that the above remarks have established the unpatentability of Claims 26 and 36 under 35 U.S.C. §112, first paragraph, and the

unpatentability of Claims 43-50 under 35 U.S.C. §102 or §103. An Office Action notifying the present Applicants of the same is respectfully solicited.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

By: Robin L. Teskin  
Robin L. Teskin  
Registration No. 35,030

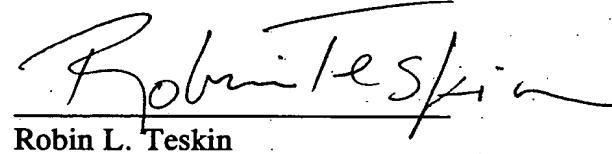
P.O. Box 1404  
Alexandria, VA 22313-1404  
(703) 836-6620

Date: December 31, 1998

**CERTIFICATE OF SERVICE**

I hereby certify that on this 31<sup>st</sup> day of December, 1998, a true and correct copy of the  
Protest Under 37 C.F.R. §1.291(a) was served via first class mail to:

David W. Hight, Esq.  
BECTON DICKINSON AND COMPANY  
One Becton Drive  
Franklin Lakes, New Jersey 07417

  
Robin L. Teskin